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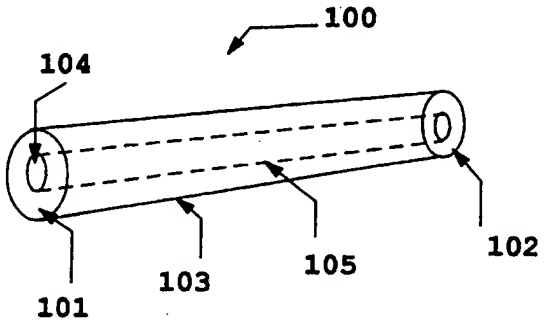
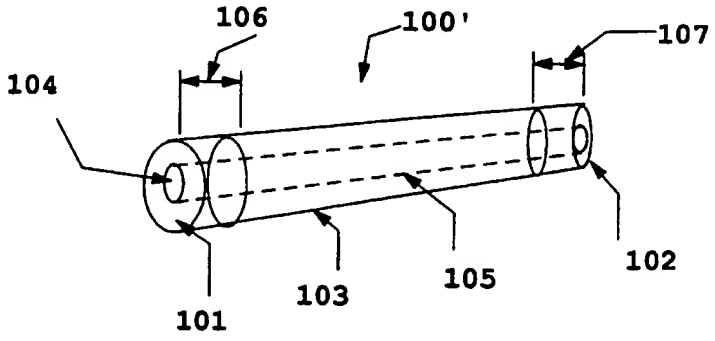
(54) Title: LUMINAL GRAFT, STENT OR CONDUIT

(57) Abstract

This invention relates to implants useful as stents for opening or strengthening biological conduits, or as grafts or conduits for replacing or connecting portions of biological tissues having a lumen. Accordingly, the implants of this invention may be applied in portions of the peripheral and coronary vascular system, biliary, urinary, esophageal, digestive, ocular, tracheal, bronchial, reproductive, and neural systems. The implant comprises a segment of bone having a lumen through at least a part thereof, and wherein at least a portion of the implant is demineralized so as to be pliable.



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# 1.0 TITLE OF THE INVENTION
# LUMINAL GRAFT, STENT OR CONDUIT

## 2.0 BACKGROUND OF THE INVENTION

### 2.1 FIELD OF THE INVENTION:

This invention relates to a novel intraluminal graft, stent, or conduit implant produced by demineralization of cortical bone having a lumen, appropriate shape and dimensions.

### 2.2 BACKGROUND:

In the field of vascular transplantation, many devices are known for opening an occluded vessel, as with a stent, or for replacing or strengthening portions of a vessel, as in bypass surgery. Various synthetic conduits for use in physiologic locations where production of a passage is desired have also been described. However, such methods typically depend on insertion into the biological milieu of a synthetic device, which typically requires removal at a later date, harvesting of autograft or allograft tissue from limited resource sites, or production of complex mixtures for preparation of the desired conduit or implant.

Examples of know methods for producing grafts, stents or conduits include the following:

#### A. Grafts:

U.S. Patent No. 5,376,110 discloses a chemically cross-linked collagenous graft material wherein physical force, stress or movement is applied during a collagen cross-linking process in order to derive desired shapes.

U.S. Patent No. 5,192,311 discloses a method for making a homograft wherein a tubular substrate having a thrombogenic surface is implanted in a blood vessel in order to permit collagenous growth to occur on the thrombogenic surface to form a vessel which is then removed from the substrate and used as a graft material.

U.S. Patent No. 4,787,900 discloses a method for making an inner layer of a multilayer blood vessel prosthesis by contacting collagen with an aminopolysaccharide and crosslinking the resulting polymer, and forming an outer layer by freeze-drying bioreplaceable material onto the inner layer.

U.S. Patent No. 5,591,225 discloses an artificial blood vessel comprising a tube of a porous synthetic polymer on which a protein or peptide having cell adhesion and growth functions is covalently bonded to encourage cellular adhesion and to prevent thrombus formation.

U.S. Patent No. 5,549,664 discloses an artificial blood vessel made from an elastomeric material wherein a first layer has closed, noncommunicating cells, and a second layer thereof has open, mutually communicating cells.

U.S. Patent No. 5,037,377 discloses a method for improving the biocompatibility of a vascular graft by using collagen to coat a biocompatible fabric which is to be contacted with blood, and then cross-linking the collagen coating.

U.S. Patent No. 3,284,557 discloses a method for "crimping" a tube of collagen for use as a vascular prosthesis, so that when bent, the collagen tube does not kink and thereby become occluded. The collagen tube was woven from "collagen yarn".

B. Stents:

U.S. Patent 5,665,116 describes a method and apparatus for catheterization to dilate a vascular blockage wherein a catheter assembly carries a balloon to a site of

vascular blockage where the balloon is expanded to uncoil a coiled ring structure having longitudinally extended struts, which is carried on the balloon, and which locks to remain in an uncoiled position to dilate the blocked vessel.

U.S. Patent Nos. 5,195,984; 5,571,171; 4,776,337; and 5,102,417; disclose various embodiments of balloon catheters for insertion of stents.

C. Conduits:

U.S. Patent Nos. 4,963,146 and 5,026,381 disclose a multi-layered, semi-permeable conduit for nerve regeneration wherein the conduit is prepared by precipitation of an aqueous dispersion of Type 1 collagen and spinning the precipitate to form a conduit which must be further compressed, frozen, lyophilized, and cross-linked, prior to use.

U.S. Patent No. 5,019,087 discloses a conduit prepared from Type 1 collagen and laminin for nerve regeneration, wherein the collagen and laminin are admixed at defined ratios.

D. Auxiliary Technology:

U.S. Patent Nos. 5,613,982 and 5,632,7798 disclose a method for reducing the immunogenicity of a collagenous implant by removing cells from a tissue to produce a tissue matrix, washing the tissue matrix to remove antigens, and treating with adhesion factors (fibronectin, heparin) to promote attachment of fibroblast cells immunologically acceptable to the intended recipient of the thus prepared implant.

U.S. Patent No. 4,597,762 discloses a collagen preparation produced by proteolyzing mammalian Type-1 collagen containing material under specific conditions, cross-linking the proteolyzed material, reducing (bleaching) the cross-linked material and sterilizing the reduced material.

U.S. Patent No. 5,507,813 discloses a shaped material derived from elongate, demineralized, bone particles having specified median lengths, and which are bonded to each other by admixture with adhesives, fillers, plasticizers, and the like.

U.S. Patent No. 5,676,146 discloses a method for radiologic tracking of an implant, such as that described in U.S. Patent No. 5,507,813, by including therein a piece of mineralized bone, which acts as a resorbable radiopaque marker.

U.S. Patent No. 5,171,273 discloses a synthetic tendon comprising aligned, cross-linked, synthetic collagen fibers embedded in a non-crosslinked collagen matrix.

U.S. Patent No. 4,923,380 discloses a method for preparing collagen tubes for use as a vascular prosthesis or nerve suture wherein aqueous collagen is "coagulated" as it is extruded in a tubular manner, followed by addition of azide, rather than glutaraldehyde, to induce "denaturation" of the collagen.

U.S. Patent No. 5,139,505 discloses a radiopaque device comprising a collagen tube with frusto-conical ends and an intermediate annular rim for assisting in suturing adjacent hollow organs (intestines, bile ducts, etc.), along with a collagen wrap to be used as a band-aid.

In view of the above art in which various forms of grafts, stents, conduits and auxiliary technology has been described, it will now better be appreciated that the present invention provides a novel device and method for meeting the continuing need for grafts, stents and conduits for biological systems by providing partially or fully demineralized bone segments having a lumen for use in these applications. Any of the known technology, including the above mentioned auxiliary technology, however, may be applied in various embodiments of the present invention in order to, for example, reduce the immunogenicity or thrombogenicity of the present device, and the above discussed art is therefore incorporated by reference for that purpose.

## 3.0 SUMMARY OF THE INVENTION

This invention relates to implants useful as stents for opening or strengthening biological conduits, or as grafts or conduits for replacing or connecting portions of biological tissues having a lumen or in which conduction of material (e.g. as a neural suture) is required. Accordingly, the implants of this invention may be applied in portions of the peripheral and coronary vascular system, ocular ,biliary, urinary, renal, esophageal, tracheal, reproductive, and neural systems. The implant comprises a segment of bone having a lumen, machined or naturally occurring, through at least a part thereof, and at least a portion of which is demineralized so as to be pliable.

## 4.0 BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 provides a side view of a tubular implant embodiment of this invention comprising a lumen and a body comprised of uniformly demineralized cortical bone (Fig. 1A) and an embodiment wherein terminal annular segments of the implant are retained in a relatively rigid, mineralized or only partially demineralized state (Fig. 1B). It should be appreciated that for some applications, there may be only one terminal annular segment that is retained in a relatively rigid mineralized or partially demineralized state, and in other embodiments, it may be preferred for the internal segment to be mineralized, with either or both terminal annular segments being demineralized.

Figure 2 provides a side view of a tubular implant embodiment of this invention comprising a lumen and a body comprised of cortical bone having demineralized longitudinal segments (Fig. 2A) and an embodiment wherein, in addition, an internal segment of the implant is fully demineralized while terminal annular segments of the implant are retained in a relatively rigid, mineralized or partially demineralized state (Fig. 2B). It should be appreciated that for some applications, there may be only one terminal annular segment that is retained in a relatively rigid mineralized or partially demineralized state, and in other embodiments. it may be preferred for the internal

segment to be mineralized, with either or both terminal annular segments being demineralized.

Figure 3 provides a side view of a tubular implant embodiment of this invention comprising a lumen and a body comprised of demineralized cortical bone wherein an annulus thereof, between the termini of the implant, is retained in a relatively rigid, mineralized or partially demineralized state, (Fig. 3A) and an embodiment wherein the annulus of mineralized bone is interrupted by a segment of demineralized bone (Fig. 3B).

Figure 4 provides a sectional view through a tubular implant embodiment of this invention comprising a lumen and a body comprised of a longitudinal segment of demineralized cortical bone along one longitudinal aspect of the implant (Fig. 4A) and an embodiment comprising two longitudinal segments along two longitudinal aspects of the implant (Fig. 4B).

Figure 5 provides side views of implants having complex webbed (Fig. 5A) or striated (Fig. 5B) patterns of demineralized bone on an implant body that is substantially retained in a mineralized state. In a further embodiment (Figs. 5C and 5D), a "coiled" structure for the implant is shown.

Figure 6 provides side views of various stages in the process of preparing a bifurcated implant of this invention by slicing and suturing a demineralized segment of the implant.

Figure 7 provides side views of various stages in the preparation of bifurcated implants according to this invention by suturing compatible implant parts to each other (Fig. 7B), or by inserting one implant segment into another implant segment, and suturing the segments together (Fig. 7C).

Figure 8 shows a device of this invention for use as a lumen junction means.

## 5.0 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In preferred embodiments of the implant of this invention, the implant comprises a body of cortical bone having a lumen through at least a portion thereof. The lumen has an internal diameter approximately matching the internal diameter of the lumen of a physiologic channel. In addition, preferably, the implant also has an external diameter allowing the implant to be inserted into the lumen of a physiologic channel, or to allow two portions of an existing physiologic channel to be connected to each other. At least a segment of the implant is relatively rigid, due to no or partial demineralization, while another portion of the implant is relatively pliable as a result of that segment having been demineralized or partially demineralized.

The source bone may be of either human (allograft or autograft) or animal origin (xenograft), or it may be derived by culture *in vitro* or from recombinant bone sources, and may be implanted into humans or animals. Those skilled in the art will recognize that, in addition to bone material, a biocompatible coating or infusate may be incorporated into or onto the implant. Various treatments may be applied to the implant, in order to: (a) reduce antigenicity or immunogenicity, (e.g. "tanning," treatment with glutaraldehyde, urea, other chaotropic agents, see the treatment of U.S. Patent Nos. 5,613,982; 5,632,778, hereby incorporated by reference, and the like); (b) reduce thrombogenicity, as in treatments with anti-thrombogenic compounds and surface treatments (e.g. by treatment with barium sulfate; see also the treatments of U.S. Patent Nos. 5,192,311; 4,787,900; 5,591,225; all of which are hereby incorporated by reference herein as potential treatments for the implant of this invention when it is to be applied as an intravascular graft, stent or conduit); (c) impart or retain radiopacity for all or a portion of the implant, to assist in positioning, orientation and tracking of the implant (e.g. see the method of U.S. Patent No. 5,676,146, and patents mentioned therein, all of which are hereby incorporated by reference for purposes of teaching production of an implant having radiopaque characteristics, bearing in mind, however, the distinction that, per the referenced 5,676,146 patent, radiopaque native, mineralized bone is added to a composite of demineralized bone particles in which the only purpose

of the mineralized bone is to provide a radiopaque marker, while in the present invention, an unitary device is disclosed in which the radiopaque, mineralized portion of the device is an integral part of the implant, and which has a functional, structural role to play, over and above the mere provision of radiopacity).

It will further be appreciated that the dimensions of the implant of this invention will be dictated by the dimensions of the implant site. For example, the implant may desirably have an internal diameter of between about 2 millimeters (e.g. for a coronary artery implantation site) to about 40 millimeters (e.g. for an aortic implantation site), with internal diameters anywhere between these extremes being desirable, depending on whether the implant is to be used as a stent, conduit or graft in connection with a large physiologic channel (e.g., the aorta) or a small channel (e.g., the vas deferens). Typically, the length of the implant will be between about 2 millimeters and about 10 centimeters, with this dimension, again being selected by the surgeon, according to the implant site where said implant is to be employed.

The structure of the implant may include a tube which is completely demineralized, a tube which has segments that are demineralized and segments that are not demineralized or which are partially demineralized, or an implant wherein only a portion thereof has a lumen therethrough. It will be recognized that the degree of demineralization dictates the level of implant flexibility, are required for particular physiologic applications or functions. In embodiments that are only partially demineralized, the advantage of increased radial strength and resistance to displacement, (radial tension), are achieved respectively due to portions of the implant that are retained in a mineralized state and the partially demineralized segments. This is important, for example, in cases where the implant is used as a stent to open an occluded blood vessel, or to prevent restenosis of an infarcted vessel. Another such application, for example, where radial rigidity would be advantageous, would be the use of the implant as a stent to prevent collapse of the urethra due to an enlarged prostate. The advantages of increased longitudinal flexibility are achieved as a result of those portions of the implant that are demineralized. Longitudinal flexibility allows the

implant to traverse convoluted vessels or passageways, and permits retention of the implant in restricted passageways which are dilated to permit insertion of the relatively rigid portions of the implant. Upon release of the dilation, the flexible portion of the implant is "pinched" by the vessel to retain the implant at its implant site.

It will be recognized by those skilled in the art that the radial tension provided by the implant of this invention is a function of several features of the graft, stent or conduit, including: the wall thickness; the total architecture of the device (i.e. its overall shape, length and diameter); and the level of demineralization of each portion of the implant. In addition, it should be recognized that the wall thickness of the implant frequently has to be balanced between the desired level of radial tension that it can provide, the flexibility of the device that is required, and the internal and external diameter requirements of the passageway to which the graft, stent or conduit is to be applied.

Typically, for purposes of insertion into an existing physiologic channel, as opposed to joining to the end of such a channel which is also contemplated herein, the implant of this invention is prepared such that upon compression, the graft, stent or conduit has an outer diameter that is smaller than the internal diameter of the vessel, channel or conduit into which it is to be inserted. Upon decompression of the implant, or in its resting state, the implant has an outer diameter that is preferably slightly larger than the internal diameter of the physiologic channel into which the implant has been inserted, such that resulting friction and elastic forces assist in retaining the graft, stent or conduit at the implant site. In the case of a coil-shaped embodiment of this invention, it is possible to insert the implant into small and even convoluted vessels, and upon insertion, the implant adopts or retains a tubular structure that resists dislocation from its implant site.

In use, the implant of this invention is applied to ameliorate a wide variety of pathophysiologic conditions. For example, the implant may be inserted into the aorta as a stent to control the ballooning of aneurysms. Smaller diameter implants may be

applied as vascular grafts to achieve coronary artery bypass. Peripheral vascular obstructive diseases, such as atherosclerosis, are ameliorated by expanding the lumen of the obstructed vessel using the implant of this invention. Esophageal, tracheal and intestinal grafts according to this invention may be used to replace portions of the esophagus, trachea, bronchi, or intestine that are removed, for example, to control cancerous growth, to control hernias, aneurysms, arterio-venous malformations (AVM's), or ulcers. Urinary, renal and biliary strictures are addressed by insertion of an appropriately sized stent according to this invention.

Those skilled in the art will recognize that where the term "stent" is used to describe the implant of this invention, the implant need not be fluid-impermeable (i.e. it may contain holes, slots or spaces throughout, so long as the radial strength is sufficient to allow the implant to act in opening up occluded vessels). Where the term "graft" is used, those skilled in the art will recognize that this implies that a portion of a physiological passage is replaced or interconnected to other such passages by means of the implant. Typically, when used as a graft, the device of this invention should be fluid impermeable, (e.g. as when the implant is used as a vascular graft), although this may not be absolutely required for all applications of the graft of this invention. Where the term "conduit" is used, those skilled in the art will appreciate that use of the implant of this invention is intended to create a passage through which physiologic processes may be directed (e.g. as in neural growth, which has heretofore been conducted through various conduits, see U.S. Patent Nos. 5,026,381; 5,019,087; 4,963,146, all of which are hereby incorporated by reference). Such conduits may be fluid permeable, fluid impermeable, or semi-permeable, depending on the particular application requirements.

Stents according to this invention are inserted via an appropriate means known in the art, such as a catheter, to strengthen a weakened vessel, for example in an aneurysm, or to open an occluded vessel, as in coronary artery stenosis. Known techniques for stent implantation may be used for the instant device, as in, for example, the balloon expandable stents known in the art as those of PALMAZ-SCHATZ® (see, for example, U.S. Patent Nos. 5,195,984; 5,571,171; 4,776,337; 5,102,417, hereby

incorporated by reference), by use of balloon expansion of vessels and insertion of the implant of this invention, by use of catheters, by surgical insertion, and the like. Grafts according to this invention may be sutured in place according to methods known in the art, as for example in coronary artery bypass surgery (e.g. open heart sternotomy), either by suturing the demineralized or partially demineralized portion, or by passing sutures around non-demineralized, relatively rigid portions of the implant, which is inserted within or attached onto the end of an existing physiologic vessel or conduit. Other means known in the art, as in use of fibrinogen "glues", use of staples, laser technology, and the like may, of course, likewise be used to affix the grafts as needed. Linear grafts, tubular grafts, bifurcated grafts, and various other conformations suggested to those skilled in the art by the specific structures disclosed herein come within the scope of this invention. Conduits and uses therefore, such as in nerve regeneration, may likewise be provided and affixed as described for the stent and graft embodiments of this invention.

Referring to figure 1, there is provided a side view of a tubular implant embodiment **100** of this invention comprising a lumen and a body comprised of uniformly demineralized cortical bone (Fig. 1A) and an embodiment **100'** wherein terminal annular segments of the implant are retained in a relatively rigid, mineralized or only partially demineralized state (Fig. 1B). The external features of the implant are machined to any desired shape prior to demineralization, and the lumen is likewise machined to any desired dimensions. In the implant **100**, the implant has termini **101** and **102**, a body **103** comprised of demineralized bone, a central bore **104**, which creates a lumen **105** running through the implant between the termini **101, 102**, or optionally, running only through a portion of the body of the implant **100**. The implant **100** is prepared by machining a segment of cortical bone to achieve a tubular structure, according to methods known in the art. A central bore **104** is either machined through at least a portion of the implant body to provide the lumen **105**, or the bore **104** may originate from a natural lumen structure, as in the natural intra-medullary canal that exists in certain bones, from which the marrow may be removed and which may be machined or otherwise treated to achieve a desirable lumen **105** diameter and surface.

The entire implant body, or a portion thereof, is then demineralized according to methods known in the art, including but no limited to acid treatment to leach the minerals from the various portion of the implant sought to be demineralized.

In the embodiment **100'** shown in Fig. 1B, the additional feature is provided wherein terminal segments **106, 107** of the implant are retained in a relatively rigid, mineralized or partially demineralized state. This feature provides a segment of the implant that acts to provide strength to the implant and a means for assisting in retention of the implant in place upon implantation. Alternatively, sutures may be sewn around the terminal segments **106, 107** and into the pliant internal segment **103** of the implant body. In this way, the termini of the implant may be sutured to adjacent vessel ends, or if inserted within a vessel, the sutures may be used to retain the implant immobile at the implant site. The relatively rigid annular segments **106, 107** are less susceptible to being ripped, as compared to the pliant, demineralized segment of the implant. Naturally, those skilled in the art will appreciate from this disclosure that only one terminal segment may be mineralized, while the other may be demineralized. Alternatively, both termini may be demineralized, and an internal portion or several discrete internal portions of the implant may be retained in a relatively rigid, mineralized or partially demineralized state. Examples of such embodiments are discussed in further detail below.

Figure 2 provides a side view of a tubular implant embodiment **200** of this invention comprising termini **201, 202**, a terminal bore **204**, a lumen **205** and a body **203** comprised of cortical bone having demineralized longitudinal segments **210, 211**, (Fig. 2A); those skilled in the art will recognize that it is a matter of application that defines the extent of demineralization and rigidity that is desired. Accordingly, the segments shown as **210, 211**, may just as well be the mineralized segment, with the remainder of the implant being demineralized. Also shown, (Fig. 2B), is an embodiment **200'** wherein, in addition, an internal segment **220** of the implant is fully demineralized while terminal annular segments **206, 207** of the implant are retained in a relatively rigid, mineralized or partially demineralized state (Fig. 2B), for a similar

purpose and effect, as described above in regard to embodiment **100'**. As noted above, in addition, the segment **220** may be the segment of the implant that is retained in the relatively rigid, mineralized or partially demineralized state, while the terminal segments **206, 207** may be the segments that are rendered pliable through demineralization.

Figure 3 provides a side view of a tubular implant embodiment **300** of this invention comprising a terminal bore **304**, a lumen **305**, termini **301, 302**, and a body **303** comprised of demineralized cortical bone wherein an annulus thereof, **320,** between the termini of the implant, is retained in a relatively rigid, mineralized or partially demineralized state, (Fig. 3A). The width **310** of the annulus may be any desired width, so as to provide an internal relatively rigid segment that provides radial strength, sufficient to retain a desired internal diameter for a vessel which, in the absence of the implant, may be occluded. In an alternate embodiment **300'**, (Fig. 3B), the annulus of mineralized bone **320'** is discontinuous, having segments of demineralized bone **330** interrupting the continuity of the mineralized annulus **320'**, thereby enhancing flexibility, while retaining radial strength. The width of the annulus, **310'**, may again be of any desired dimension.

Figure 4 provides a sectional view through a tubular implant embodiment **400** of this invention comprising a lumen **404** and a body **403** comprised of a longitudinal segment **402** of demineralized cortical bone along one longitudinal aspect of the mineralized wall **401** of the implant (Fig. 4A). In a further embodiment **400'**, the implant comprises two longitudinal demineralized segments **402** along two longitudinal aspects of the implant (Fig. 4B). These sectional views are representative of the cross sectional composition of the implants shown in figure 2. The significance of the longitudinally demineralized segments of these embodiments is that they provide compressive flexibility to the implant which otherwise is longitudinally rigid due to the mineralized body of the implant. This feature would be helpful, for example, where the implant must be compressed in order to hold the stent, graft or conduit of this invention in its correct position and alignment within a vessel into which it is inserted.

Figure 5 provides side views of implant embodiments **500, 500'** having complex webbed (Fig. 5A) or striated (Fig. 5B) patterns of demineralized bone on an implant body that is substantially retained in a mineralized state. These implant embodiments are useful in specific applications such as replacement of tracheal segments, where a considerable amount of rigidity is required at the same time that flexibility is also necessary, or where a long lesion exists within a vessel, requiring a stent with a large surface area, strength, and flexibility. To this end, in a further embodiment of this invention, the implant may have a coiled structure (see Fig. 5C), which in a resting state, has a tubular structure, **500"**. In this embodiment, a segment of bone, having a diameter **A,** is machined in such a fashion that a spiral cut **505** in the bone is effected, the thus machined bone is then demineralized, allowing for extension of the implant into an extended, thin, coiled implant, **500"'**(see Fig. 5D), having a smaller diameter **B**, and which has the natural tendency to retract into a tubular structure, having the diameter **A**. Depending on the degree of demineralization of this embodiment of the implant, increasing levels of strength and flexibility may be retained in all or defined parts of the implant.

In all of the above described embodiments of the implant of this invention, cortical bone segments are machined to the desired proportions, a lumen is drilled through at least a portion of the implant (unless the source bone already has an acceptable lumen or canal running through at least a portion thereof and which may be machined, as needed, to the desired proportions), and then portions of the implant are demineralized by treatment with, for example, 0.5 to 0.75 N hydrochloric acid, EDTA, or other leaching solvents known in the art. Treatment of the bone with waxy barriers, solvent impervious protective layers and the like are employed to achieve even the most complex of demineralization patterns. In addition, it will be appreciated by those skilled in the art that bone segments having a natural bore running therethrough, as with the intramedullary canal of the femur, tibia, fibia and the like, may be harvested and further machined to provide the appropriate shapes and dimensions as described herein after removal of bone marrow. Such bone sources are limited to production of conduits, however, which have rather large internal and external diameters, and may

therefore be used only for provision of stents, grafts or conduits for some of the larger physiologic passages, such as the intestine, aorta and the like. Smaller segments of bone are therefore machined to provide the lumen where smaller internal and external diameter grafts, stents or conduits are required, and where appropriate, such machining may be achieved by drilling and the like, or by use of an appropriate laser.

To provide variegated patterns of demineralization, as shown in figures 5A and 5B, a novel device and demineralization method, exemplified in figure 5E, may be employed. According to this method, a segment of bone machined to desired proportions of length, and diameter to form the implant **510**, including a lumen **511**, is adapted with a tightly-fitting, internal tube **512**, made from a fluid impermeable material (plastic, silicone, polyethylene, and the like), having defined therein a pattern **513** cut into and through the walls of the tube **512**. The external diameter **A** of the inner tube is chosen to closely match (i.e. be slightly smaller than) the internal diameter **A** of the implant **510**.

The shape of the cut-out pattern **513** matches the pattern which is intended to be transferred to the implant as a pattern of demineralization. The tube **512**, has a bore **514**, into which and through which demineralization solution, such as acid, may be made to flow. Upon fitting the tube **512** into the lumen **511** of the implant, passage of demineralization solution therethrough permits demineralization of the implant **510** from the inside, to create the desired demineralization pattern therein.

To make enhance the efficiency of the demineralization process, the pattern of demineralization may be imparted to the exterior of the implant **510** at the same time that the implant is partially demineralized from the inside. This is achieved by inserting the entire implant **510** with the tube **512** inserted therein into an outer tube **520**. The internal diameter **B** of the outer tube **520** is selected such that it closely matches (i.e. is only slightly larger than) the external diameter **B** of the implant **510**. This outer tube **520** is also made from a fluid impermeable material. A pattern **521**, matching that cut out in the walls of the tube **512**, is cut out into and through the walls of the tube **520**. In

order to keep the patterns of the tubes **512** and **520** in register with each other, at one or both ends of the tube **512**, a registration means **515**, including marks, grooves or projections, is provided which fit with a complementary registration means **522** provided in the outer tube **520**. Accordingly, the implant carrying the internal tube **512** can only be inserted into the outer tube **520** in such an orientation as to cause the pattern **513** to align perfectly with the pattern **521**. The implant **510** is also matched with an outer tube **520** such that a tight fit or seal is created between the external walls of the implant **510** and the internal walls of the tube **520**. If needed, this seal may be enhanced by use of silicone caulk or the like. The outer tube **520** with the implant **510** inserted therein and having the internal tube **512** inserted therein is then inserted through a sealable aperture **530** of a demineralization bath **535**. The bath **535** is filled with a demineralization solution, such as acid, and the pattern of demineralization is permitted to become defined for an appropriate length of time, defined by the thickness of the implant **510** and the strength of the demineralization solution. The interior of the the implant may be exposed to demineralization solution by keeping the end **523** of the implant open such that demineralization solution flows into the interior of the inner tube **512**. The end **524** may be stoppered, or adapted with hose and a pump, which causes the demineralization to flow through the inner tube **512** and back into the demineralization bath **535**. In this manner, any desired pattern of demineralization may be imparted to the implant. By adapting this method to various shapes of protective means, any type of demineralization may be defined in a bone implant of essentially any shape.

In order to provide conduits having branched or bifurcated structures, implant segments according to this invention are cut, sutured, or joined. Figure 6 provides side views of various stages in the process of preparing a bifurcated implant **660** of this invention by slicing and suturing a demineralized segment of an implant **600** according to this invention. According to this method, the implant **600** is demineralized over the segment **610**, while retaining a segment **620** in a mineralized state. Alternatively, the segment **620** may likewise be demineralized. In either case, the demineralized segment

**610** is cut along a longitudinal axis of the implant (Fig. 6A), to produce an intermediate device (Fig. 6B) having two semi-detached segments **640, 650**. Each semi-detached segment is folded upon itself and held in the folded state by sutures **690,** or like means, to provide a bifurcated conduit **660** having two channels **680, 670** (Fig. 6C).

In another embodiment of this invention, bifurcated vessels **730, 740** are produced by implant segments **700, 720** of this invention. In one aspect, the implant segment **720** is cut to produce an entry-way **721** along a medial, demineralized aspect of the implant. The implant **701** is at least partially demineralized such that a terminal aspect **701** thereof is pliant. As shown in Fig. 7B, the thus prepared implant elements are then affixed to each other, by suturing or like means, to provide the bifurcated structure **730**, composed of elements **700'** and **720'** connected at the entryway **731** cut in element **720'**. In an alternate method (Fig. 7C), side holes **702, 703** are cut into the implant **700** to produce element **700"**. Thus prepared, element **700"** is inserted through the entryway **721** in element **720'** and retained in place by sutures **741** or like means. In either embodiment, **730, 740**, fluid, cells or other biological processes directed through conduit **720'**, are likewise directed through conduits **700'** or **700"**.

In figure 8, a device **800** according to the present invention, for use as a conduit or a junction means, is disclosed. This device has a similar structure and purpose to a device disclosed in U.S. Patent No. 5,139,505 for suturing hollow organs. However, the present device is made from a distinct material and by the distinct method of the present invention and is therefore much different to the device of the referenced patent. Per the present invention, a portion of cortical bone is machined to exhibit an inner surface **801** an outer surface **802** with frusto-conical ends, and an intermediate rim **803**. The ends **804, 805** of the device **800** may be demineralized to provide flexibility which may aid in insertion of the ends **804, 805** into the adjacent lumen of vessels, including blood vessels or other existing physiologic conduit. to be joined, while the rim **803** may be retained in a relatively rigid, mineralized or partially demineralized state. Alternatively, the ends **804, 805** may be retained in a relatively rigid mineralized or

partially demineralized state, while the rim **803** may be demineralized or partially demineralized. Variations on the basic structure disclosed herein are, likewise, contemplated by the present invention, such as for example, provision of a series of holes around the periphery of the rim **803**, through which sutures in the adjacent ends of the vessels to be joined are passed, thereby affixing the vessel ends to the rim **803** of this embodiment of the device of this invention.

Those skilled in the art will recognize that in any of the above described embodiments of this invention, various treatments may be applied to the implant to reduce antigenicity or immunogenicity, by tanning with glutaraldehyde, treatment with azide, or the like, to reduce thrombogenicity, by coating of the implant with collagen, siloxane (and the like surface treatments, to reduce porosity), immunologically acceptable cells or cell products or by culturing the implant in the presence of such cells as fibroblasts, sertoli cells, endothelial cells or smooth muscle cells, or the like, and to increase bioactivity, as in coating or soaking the graft, conduit or stent of this invention with growth factors, or phospholipids, and the like or culturing the implant with sertoli cells to enhance neural growth, culturing the implant with endothelial cells, to provide a conduit acceptable for implantation in the lumen of the intestine, or culturing the implant with smooth muscle cells, to provide a contractile cellular surface to the implant.

Having generally and specifically described the implant of this invention, including its best mode, the invention to which an exclusive right is claimed is set forth in the claims which follow.

## 6.0 WHAT IS CLAIMED IS:

1. An implant comprising a luminal graft, stent or conduit for implantation in or connecting portions of a body part having a lumen or at a physiologic location where the presence of a conduit is beneficial, wherein said implant comprises a segment of cortical bone, said bone segment comprising a bore or lumen running through at least a portion thereof, and wherein at least a portion of said segment of cortical bone is demineralized such that said segment is flexible.

2. The implant of claim 1 implanted within or connecting one or more blood vessels.

3. The implant of claim 2 wherein said one or more blood vessels is a vein, or an artery.

4. The implant of claim 1 implanted within or connecting one or more ducts, vessels or passages.

5. The implant of claim 4 wherein said one or more ducts or passages are selected from a bile duct, an hepatic duct, a renal duct, an urethral duct, an ureter, a vas deferens, a fallopian tube, an exocrine glandular duct, a lymphatic duct, the esophagus, the trachea, a bronchial passage, and the intestine.

6. The implant of claim 1 having an inner surface, an outer surface, with frusto-conical ends, and an intermediate rim.

7. The implant of claim 6 wherein said ends are demineralized to provide flexibility in insertion of the ends into the adjacent lumen of vessels to be joined and said rim is retained in a relatively rigid, mineralized or partially demineralized state, or wherein said ends are retained in a relatively rigid mineralized or partially

demineralized state and said rim is demineralized or partially demineralized, or wherein said implant is demineralized or partially demineralized throughout.

8. The implant of claim 1 implanted between the ends of a severed nerve so as to provide a conduit for neural growth.

9. The implant of claim 1 having a tubular, coiled or bifurcated structure.

10. The implant of claim 1 having a collagen coating, a siloxane coating, a cellular coating, having been treated with growth factors or phospholipids or having been cultured with a specific cell type.

11. The implant of claim 10 cultured with sertoli cells.

12. The implant of claim 10 cultured with endothelial cells.

13. The implant of claim 10 cultured with smooth muscle cells.

14. The implant of claim 1 comprising a tube of uniformly demineralized cortical bone having a natural lumen or a lumen machined therein.

15. The implant of claim 1 comprising at least one terminal segments retained in a mineralized state and at least one internal demineralized segment, or at least one terminal segment that is demineralized and at least one internal segment that is retained in a mineralized or partially demineralized state.

16. The implant of claim 1 having at least one longitudinally demineralized segment.

17. The implant of claim 16 comprising terminal segments that are retained in a mineralized state.

18. The implant of claim 1 comprising a tube of demineralized bone having a lumen and at least one internal relatively rigid annulus or segment, circumferentially complete or incomplete, of mineralized bone.

19. The implant of claim 1 comprising a tube of bone having a lumen wherein said bone has a webbed, coiled or striated pattern of demineralized segments.

20. The implant of claim 1 wherein at least a portion thereof is radiopaque.

21. The implant of claim 1 treated so as to have a reduced antigenicity, immunogenicity, or thrombogenicity.

22. A method of making an implant which comprises machining cortical bone to the desired shape and dimensions, and, unless a natural lumen is already present in the bone, machining a lumen through at least a portion thereof, and demineralizing at least a portion of the thus machined bone to form a luminal graft, stent or conduit.

23. The method of claim 22 wherein said machining includes reducing the outer diameter of said implant such that the final outer diameter thereof is approximately the same or is slightly larger than the internal diameter of a non-occluded portion of the physiologic passage to which or into which said implant is to be applied.

24. The method of claim 22 further comprising attaching demineralized portions of one implant to another to form a bifurcated implant structure.

25. The method of claim 22 further comprising cutting a demineralized longitudinal aspect of said implant and affixing folded-over lobes thereof to each other to produce a bifurcated structure.

26. The method of claim 22 further comprising machining a spiral cut into a segment of bone, and demineralizing or partially demineralizing the thus machined bone.

27. The method of claim 22 wherein said demineralizing is achieved by sealingly inserting a fluid impermeable means within said implant, said fluid impermeable means having a pattern cut out of the walls thereof in the desired pattern in which said implant is to be demineralized, and exposing the interior of said implant to a demineralization solution which is permitted to enter or flow through said fluid impermeable means.

28. The method of claim 22 wherein said demineralizing is achieved by sealingly inserting said implant into a fluid impermeable means, said fluid impermeable means having a pattern cut out of the walls thereof in the desired pattern in which said implant is to be demineralized, and exposing the exterior of said fluid impermeable means to a demineralization solution.

29. A method for implanting into or connecting portions of body parts having a lumen or creating a lumen at a physiologic location where the presence of a conduit is beneficial, which comprises inserting a stent into said lumen, attaching a graft to or into said lumen, or creating a passage using a conduit, wherein said graft, stent, or conduit comprises a segment of cortical bone, said bone segment comprising a bore or lumen running through at least a portion thereof, and wherein at least a portion of said bone segment is demineralized such that said segment is flexible.

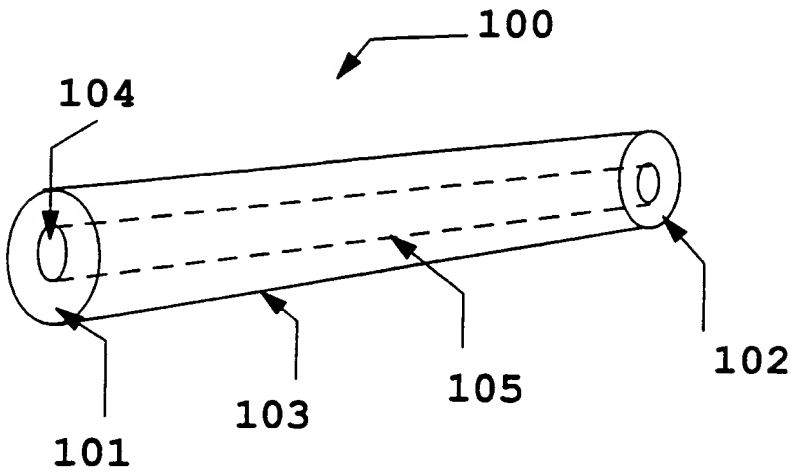


Fig. 1A

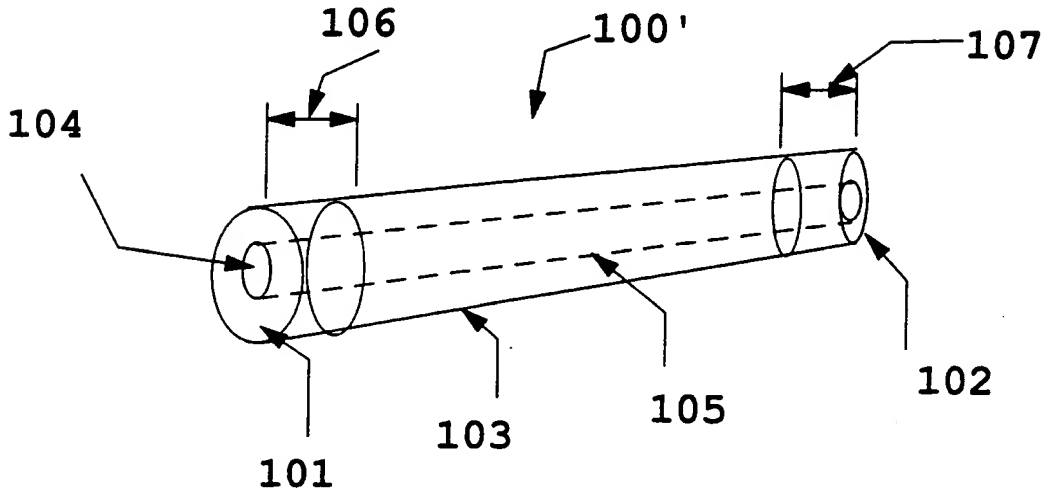


Fig. 1B

Figure 1

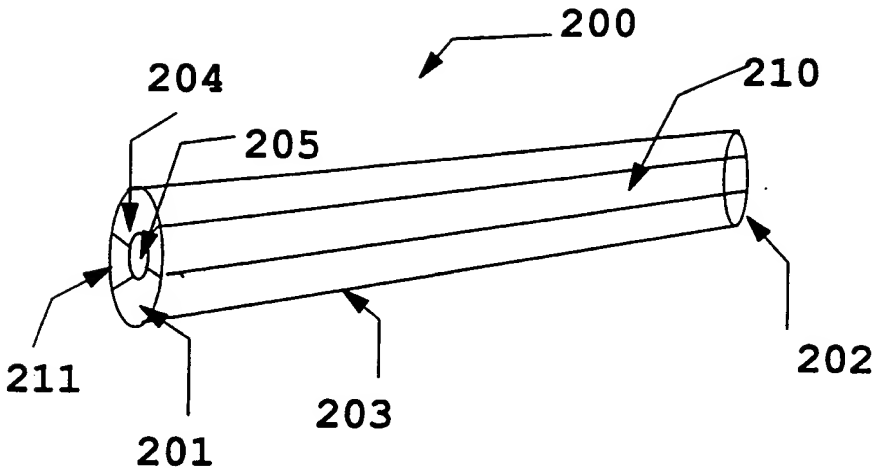


Fig. 2A

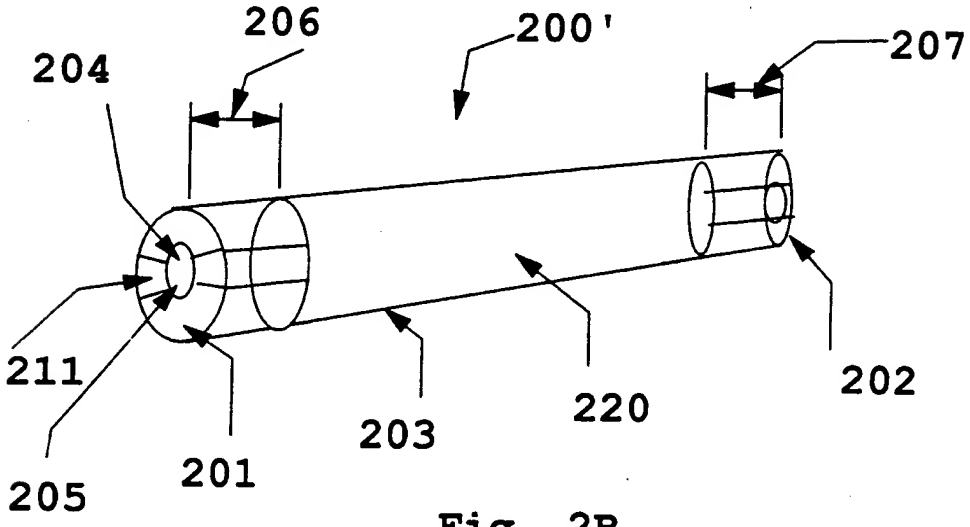


Fig. 2B

Figure 2

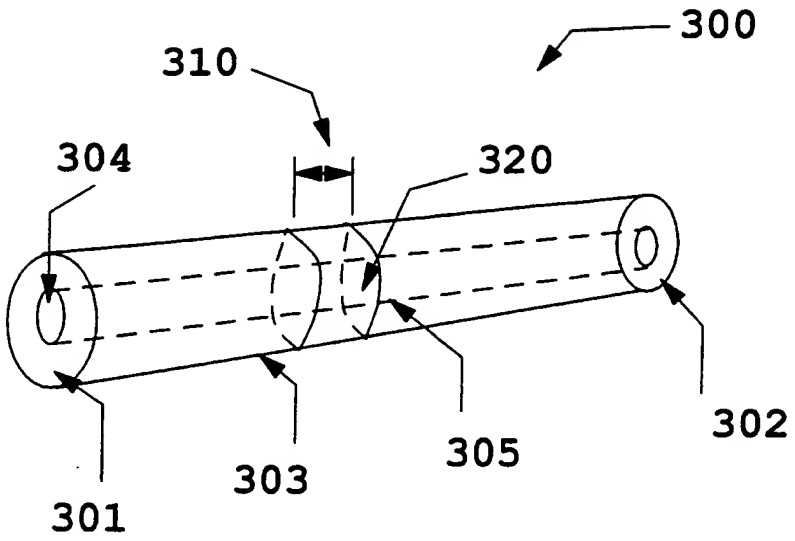


Fig. 3A

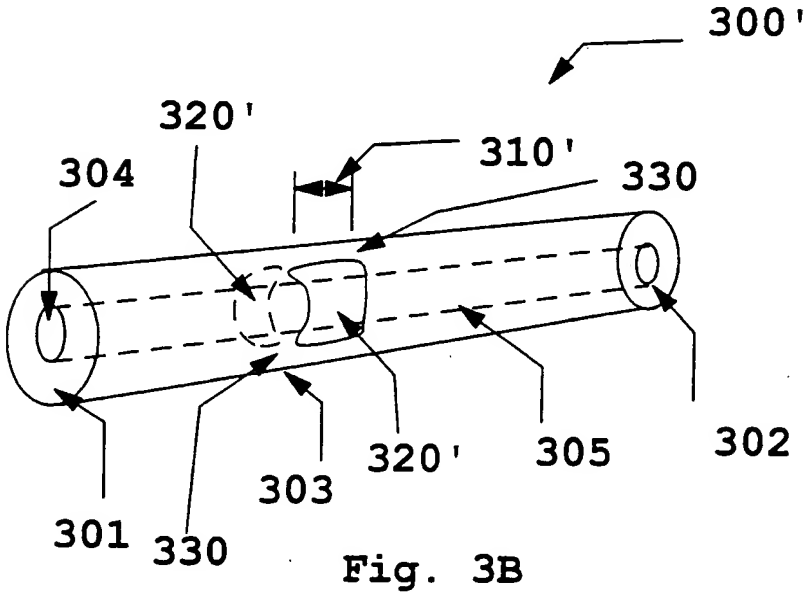


Fig. 3B

Figure 3

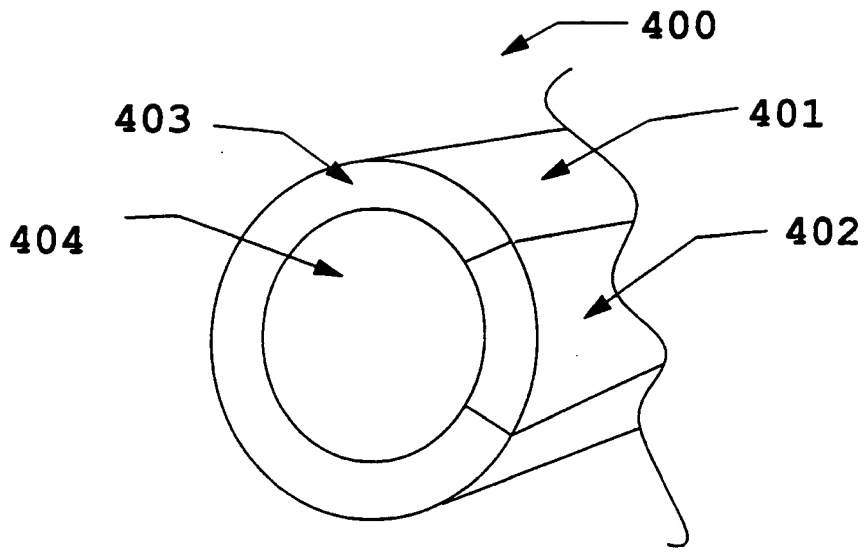


Fig. 4A

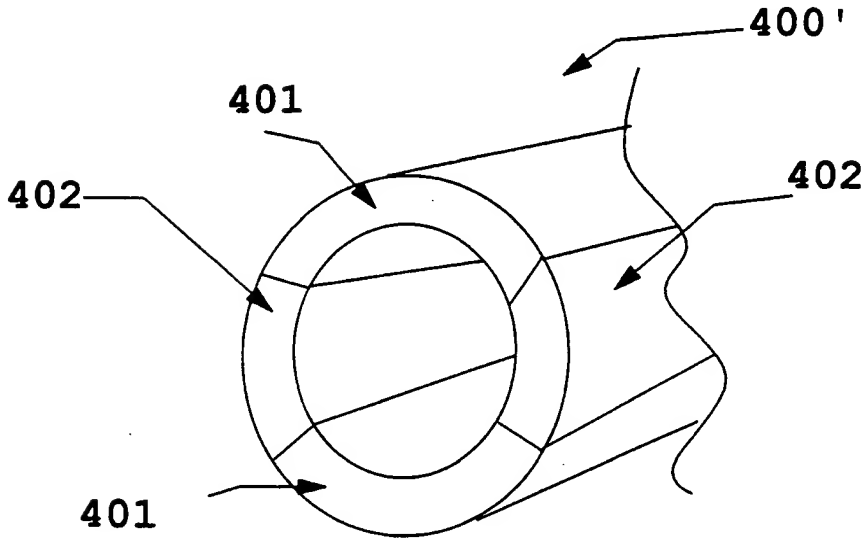


Fig. 4B

Figure 4

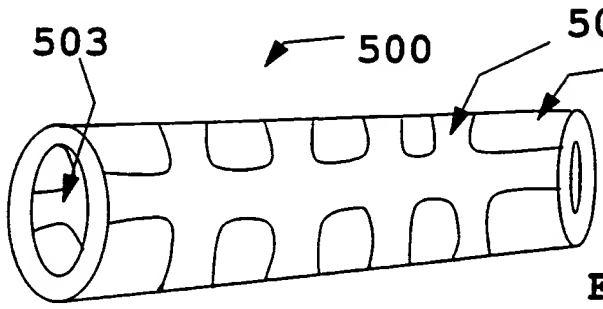


Fig. 5A

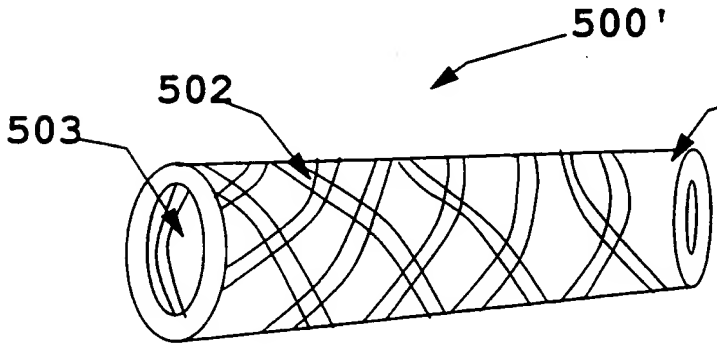


Fig. 5B

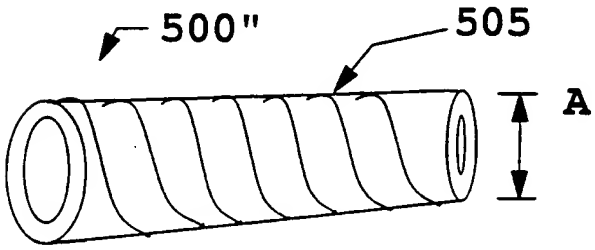


Fig. 5C

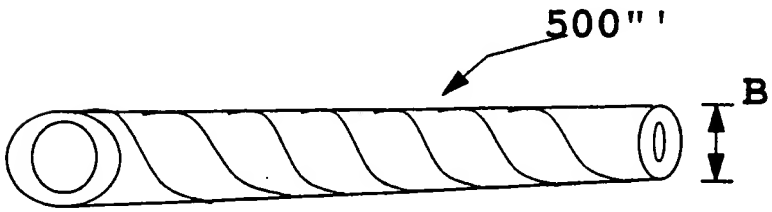


Fig. 5D

Figure 5

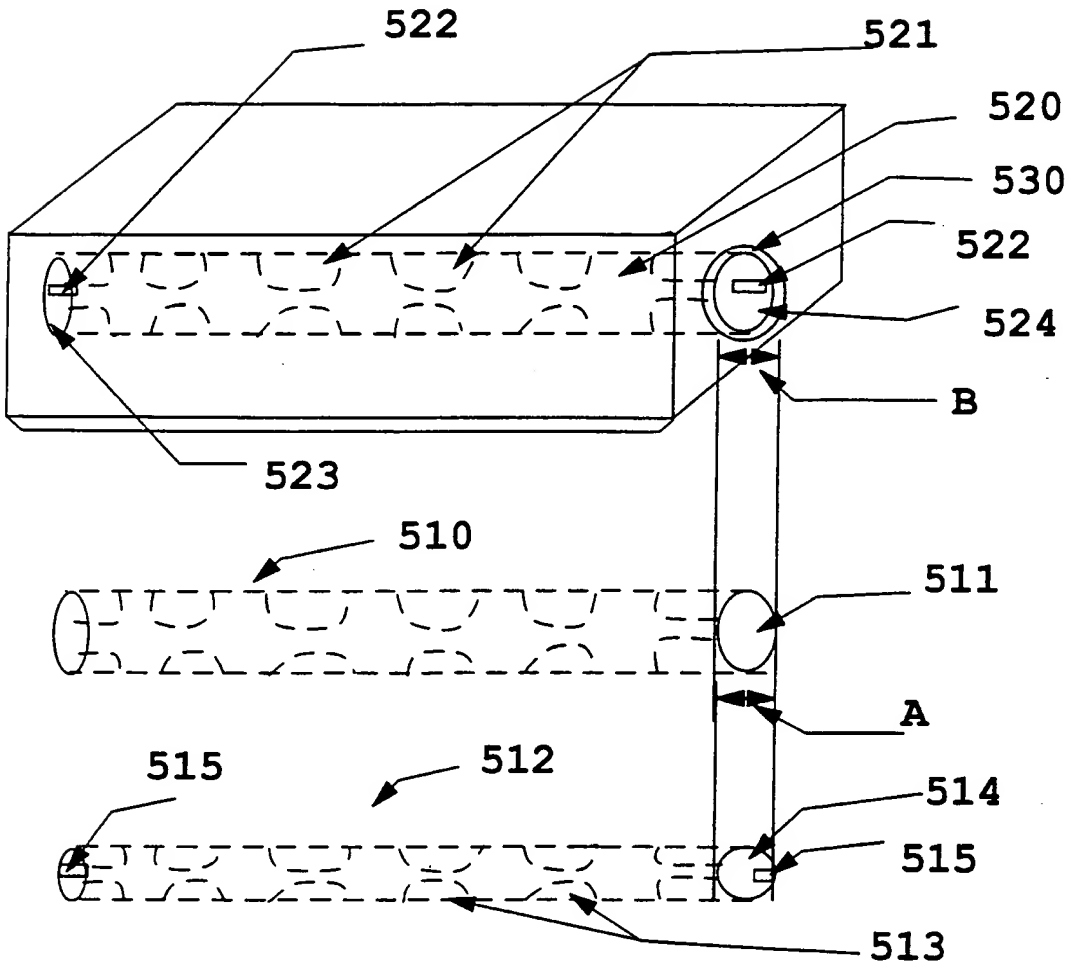


Figure 5E

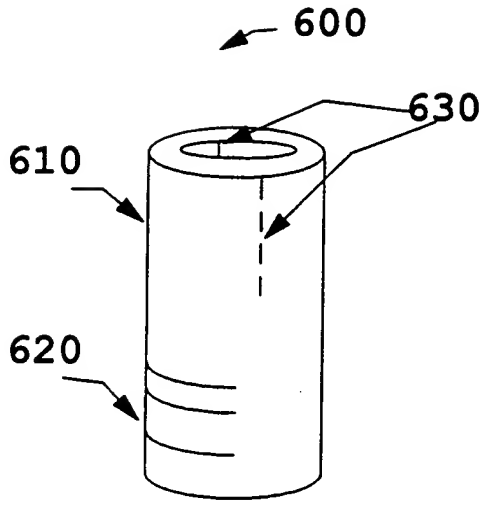


Fig. 6A

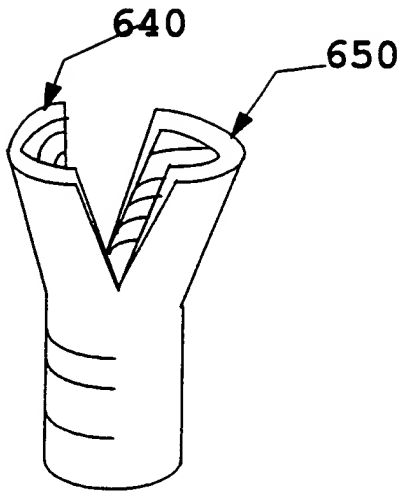


Fig. 6B

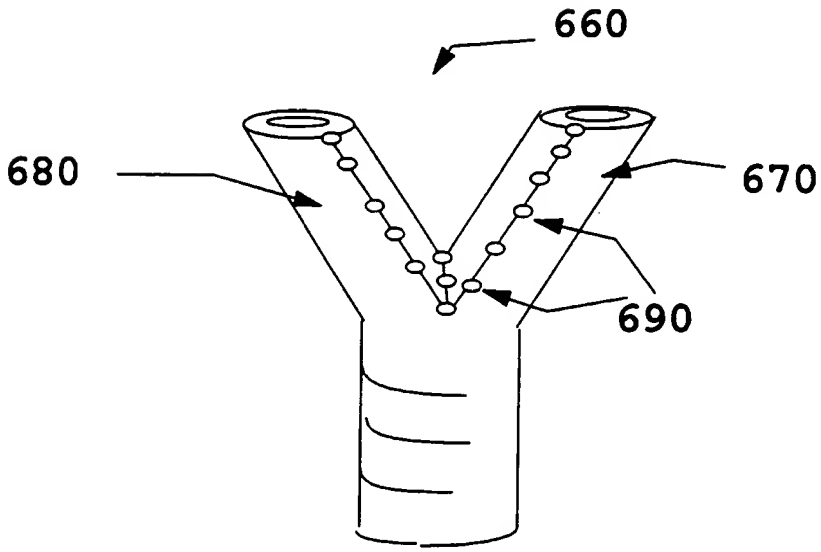


Fig. 6C

Figure 6

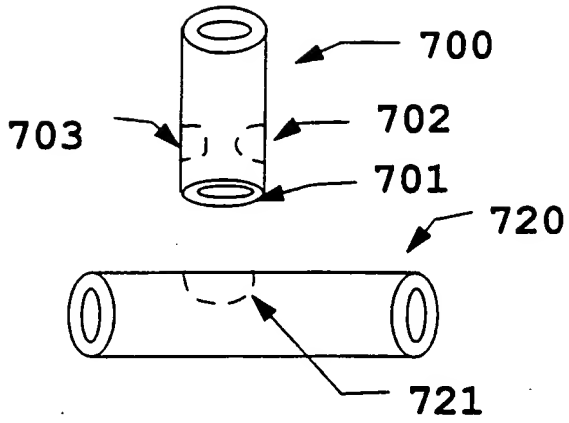


Fig. 7A

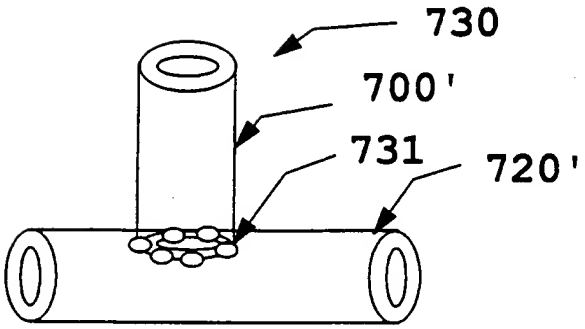


Fig. 7B

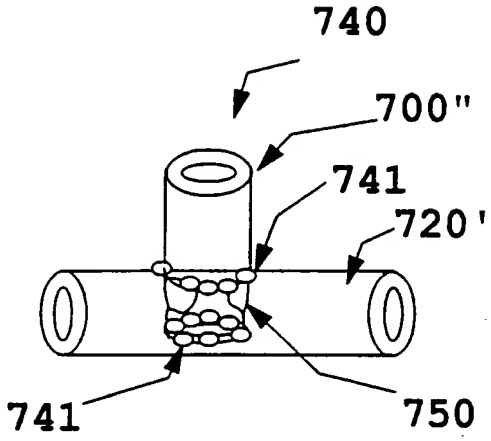


Fig. 7C

Figure 7

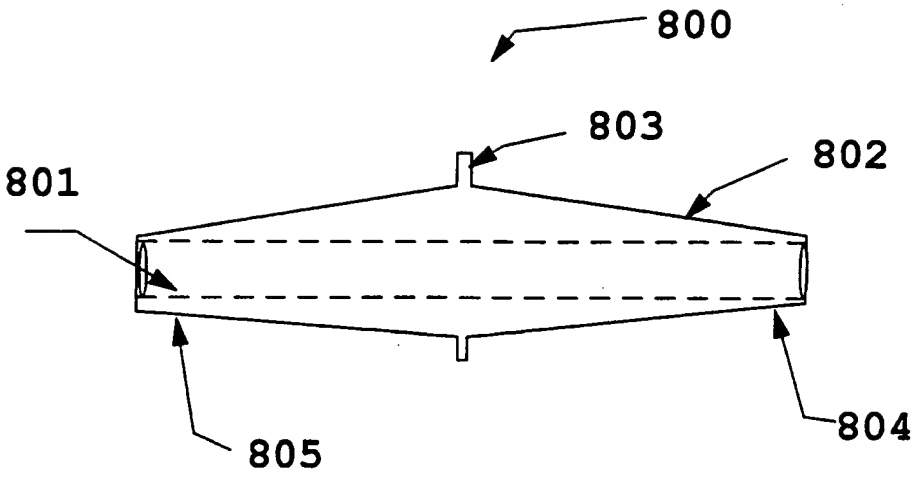


Figure 8

# INTERNATIONAL SEARCH REPORT

Interna .al Application No
PCT/US 99/01937

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61F2/04 A61F2/06 A61L27/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61F A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US 5 053 049 A (CAMPBELL TODD D)<br>1 October 1991 (1991-10-01)<br>claims | 1,22 |
| A | EP 0 483 944 A (GENDLER EL)<br>6 May 1992 (1992-05-06)<br>abstract; figure 1 | 1,22 |
| A | US 4 932 973 A (GENDLER EL)<br>12 June 1990 (1990-06-12)<br>abstract | 1,22 |
| A | US 5 139 505 A (PALMIERI BENIAMINO)<br>18 August 1992 (1992-08-18)<br>cited in the application<br>abstract; figures | 1 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 14 July 1999 | 21/07/1999 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Kanal, P |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Int. ational application No.
PCT/US 99/01937

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: CLAIM:29
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/US 99/01937

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| | | FR 2582516 A | 05-12-1986 |
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